IMPORTANT: PLEASE READ

INCLUDING PATIENT MEDICATION INFORMATION

PrRYBREVANT®

amivantamab for injection

HEALTHCARE PROFESSIONAL INFORMATION

ABBREVIATED PACKAGE INSERT

CONSULT FULL PRODUCT MONOGRAPH FOR COMPLETE PRESCRIBING INFORMATION

PrRYBREVANT, indicated:

- for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal-growth factor receptor (EGFR) Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy,

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for RYBREVANT please refer to Health Canada's Notice of Compliance with conditions - drug products web site.

RYBREVANT, indicated:

- in combination with carboplatin and pemetrexed for the treatment of patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with osimertinib,
- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) with activating epidermal-growth factor receptor (EGFR) Exon 20 insertion mutations,

have been issued a market authorization **without conditions**.

1 Indications

RYBREVANT (amivantamab for injection) is indicated:

- in combination with carboplatin and pemetrexed for the treatment of patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) with epidermal-growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with osimertinib.

A validated test is required to identify EGFR Exon 19 deletion or Exon 21 L858R substitution mutation-positive status prior to treatment (see 4.1 Dosing Considerations).

- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with activating EGFR Exon 20 insertion mutations.

A validated test is required to identify EGFR Exon 20 insertion mutation-positive status prior to treatment (see 4.1 Dosing Considerations).

- as monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.

Clinical effectiveness of RYBREVANT monotherapy is based on objective response rate (ORR) and duration of response (DOR) from a single-arm trial in patients with activating epidermal-growth factor receptor (EGFR) Exon 20 insertion mutations.

A validated test is required to identify EGFR Exon 20 insertion mutation-positive status prior to treatment (see 4.1 Dosing Considerations).

1.1 Pediatrics:

- Based on the data submitted and reviewed by Health Canada, the safety and efficacy of RYBREVANT in pediatric patients (<18 years of age) has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics:

- No clinically relevant differences in effectiveness were observed between elderly patients (≥65 years of age) and younger patients. Evidence from the clinical studies suggests that the use in the geriatric population is associated with differences in safety (see 7.1.4 Geriatrics).

2 Contraindications

RYBREVANT is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.

4 Dosage and Administration

4.1 Dosing Considerations

- RYBREVANT should be administered by a healthcare professional with appropriate medical support to manage infusion related reactions (IRRs) if they occur (see 7 Warnings and Precautions).
- When considering the use of RYBREVANT, before treatment initiation the presence of an EGFR Exon 19 deletion, Exon 21 L858R substitution, or Exon 20 insertion mutation is

required to be determined using a validated test (see Product Monograph 14 Clinical Trials).

- Administer pre-infusion medications (see 4.2 Recommended Dose and Dosage Adjustment, Table 4).
- Administer RYBREVANT via peripheral line for all Cycle 1 doses to reduce the risk of infusion related reactions (see 4.4 Administration).
- Administer diluted RYBREVANT intravenously according to the infusion rates in Table 1 and Table 3, with the initial dose as a split infusion in Week 1 on Day 1 and Day 2.

4.2 Recommended Dose and Dosage Adjustment

It is recommended that patients are treated with RYBREVANT until disease progression or unacceptable toxicity (see 4.4 Administration). Pre-medications should be administered before each RYBREVANT infusion as recommended (see Recommended Pre-infusion medications and Table 4).

RYBREVANT in combination with carboplatin and pemetrexed

The recommended dosage of RYBREVANT, when used in combination with carboplatin and pemetrexed is provided in Table 1 (see infusion rates in Table 7).

When used in combination with carboplatin and pemetrexed, RYBREVANT should be administered after carboplatin and pemetrexed in the following order: pemetrexed, carboplatin and then RYBREVANT (see Table 2).

Table 1: Recommended Dose and Dosing Schedule for RYBREVANT when in combination with carboplatin and pemetrexed

Body weight at Baseline[a]	Recommended Dose	Schedule	Number of 350 mg/7 mL RYBREVANT Vials/dose
Less than 80 kg	1400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1 • Weeks 5 and 6 – no dose	4
	1750 mg	**Every 3 weeks starting at Week 7 onwards**	5
Greater than or equal to 80 kg	1750 mg	Weekly (total of 4 doses) for Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1 • Week 5 and 6 – no dose	5
	2100 mg	**Every 3 weeks starting at Week 7 onwards**	6

[a] Dose adjustments not required for subsequent body weight changes.

Table 2: Recommended order of administration and regimen for RYBREVANT in combination with carboplatin and pemetrexed

RYBREVANT in Combination with Carboplatin and Pemetrexed		
Administer the regimen in the following order: pemetrexed first, carboplatin second and RYBREVANT last.		
Drug	**Dose**	**Duration/Timing of Treatment**
Pemetrexed	Pemetrexed 500 mg/m^2 intravenously Refer to the pemetrexed Product Monograph for complete information.	Every 3 weeks, continue until disease progression or unacceptable toxicity.
Carboplatin	Carboplatin AUC 5 intravenously Refer to the carboplatin Product Monograph for complete information.	Every 3 weeks for up to 12 weeks.
RYBREVANT	RYBREVANT intravenously See Table 1.	Every 3 weeks, continue until disease progression or unacceptable toxicity.

RYBREVANT monotherapy

The recommended dosage of RYBREVANT monotherapy is provided in Table 3 (see infusion rates in Table 8).

Table 3: Recommended Dose and Dosing Schedule for RYBREVANT monotherapy

Body weight at Baseline[a]	**Recommended Dose**	**Dosing Schedule**	**Number of 350 mg/7 mL RYBREVANT Vials/dose**
Less than 80 kg	1050 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	3
		Every 2 weeks starting at Week 5 onwards	
Greater than or equal to 80 kg	1400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	4
		Every 2 weeks starting at Week 5 onwards	

[a] Dose adjustments not required for subsequent body weight changes.

Recommended Pre-infusion medications

Two days before the first (initial) infusion only:

Oral dexamethasone or equivalent

Starting two days prior to the initial RYBREVANT infusion, patients should receive 8 mg dexamethasone orally, twice daily (total 16 mg per day). On the day of the initial infusion

(Week 1, Day 1), patients should receive 8 mg dexamethasone orally, one hour prior to infusion in addition to intravenous dexamethasone to further reduce the risk of IRR.

Day of initial and subsequent Infusions:

Prior to the initial infusion of RYBREVANT (Week 1, Days 1 and 2), administration of antihistamines, antipyretics, and glucocorticoids is required to reduce the risk of IRRs as described in Table 4. For subsequent doses, administer both antihistamines and antipyretics prior to all infusions, and glucocorticoids as necessary. Administer antiemetics as needed. After prolonged dose interruptions of RYBREVANT, restart the premedications upon reinitiation of treatment: intravenous dexamethasone, diphenhydramine, and acetaminophen (see Table 4).

Table 4: Pre-Medications

Medication	Dose	Route of Administration	Dosing Window Prior to RYBREVANT Administration
Antihistamine*	Diphenhydramine (25 to 50 mg) or equivalent	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Antipyretic*	Acetaminophen (650 to 1,000 mg)	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid‡	Dexamethasone (20 mg) or equivalent	IV	60 to 120 minutes
Glucocorticoid+	Dexamethasone (10 mg) or equivalent	IV	45 to 60 minutes

* Required at all doses.
‡ Required at initial dose (Week 1, Day 1)
+ Required at second dose (Week 1, Day 2); optional for subsequent doses

Dose Modifications

The recommended RYBREVANT dose reductions for adverse reactions (see Table 6) are outlined in Table 5.

Table 5 : RYBREVANT Dose Reductions for Adverse Reactions

Dose*	1st Dose Reduction	2nd Dose Reduction	3rd Dose Modification
1050 mg	700 mg	350 mg	Discontinue RYBREVANT
1400 mg	1050 mg	700 mg	
1750 mg	1400 mg	1050 mg	
2100 mg	1750 mg	1400 mg	

* Dose at which the adverse reaction occurred

Table 6: Dose Modifications for Adverse Reactions

Adverse Reaction	Severity	Dose Modification
Infusion Related Reactions (IRRs) (see 7 Warnings and Precautions)	Grade 1 to 3	• Interrupt RYBREVANT infusion at the first sign of IRRs. Monitor patients until symptoms resolve. • Additional supportive medications (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) should be administered as clinically indicated. • Upon resolution of symptoms, resume infusion at 50% of the previous rate. • If there are no additional symptoms, the rate may be increased per the recommended infusion rate (see Table 7 and Table 8). • Pre-medications should be administered prior to the next dose (see Table 4).
	Recurrent Grade 3 or any Grade 4	Permanently discontinue RYBREVANT
Interstitial Lung Disease (ILD) / Pneumonitis (see 7 Warnings and Precautions)	Suspected ILD/ pneumonitis (any Grade)	Withhold RYBREVANT
	Confirmed ILD/ pneumonitis (any Grade)	Permanently discontinue RYBREVANT
Skin and Nail Reactions (see 7 Warnings and Precautions)	Grade 1	• Supportive care should be initiated. • Reassess after 2 weeks.
	Grade 2	• Supportive care should be initiated. • If there is no improvement after 2 weeks, consider reducing the dose (see Table 5).
	Grade 3	• Supportive care should be initiated. • Withhold RYBREVANT until the adverse reaction improves. Upon recovery to ≤ Grade 2, resume RYBREVANT at reduced dose (see Table 5). • If no improvement within 2 weeks, permanently discontinue treatment.
	Grade 4, and severe bullous, blistering, or exfoliating skin	Permanently discontinue RYBREVANT

Adverse Reaction	Severity	Dose Modification
	conditions, including toxic epidermal necrolysis (TEN)	
Other Adverse Reactions (see Product Monograph 8 Adverse Reactions)	Grade 3	• Withhold RYBREVANT until adverse reaction improves to ≤ Grade 1 or baseline. • Resume at same dose if recovery occurs within 1 week. • Resume RYBREVANT at reduced dose (see Table 5) if recovery occurs after 1 week. • Permanently discontinue RYBREVANT if recovery does not occur within 4 weeks.
	Grade 4	• Withhold RYBREVANT until adverse reaction improves to ≤ Grade 1 or baseline. • Resume at reduced dose (see Table 5) if recovery occurs within 4 weeks. • Permanently discontinue RYBREVANT if recovery does not occur within 4 weeks. • Permanently discontinue RYBREVANT for recurrent Grade 4 reactions.

Recommended Dose Modifications for Adverse Reactions for RYBREVANT in Combination with Carboplatin and Pemetrexed

When administering RYBREVANT in combination with carboplatin and pemetrexed, follow the recommended dose modifications for adverse reactions for RYBREVANT as shown in Table 6. Refer to the Product Monographs for carboplatin and pemetrexed for their dosage modification recommendations.

Renal impairment

No formal studies of RYBREVANT in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses, no dosage adjustment is necessary for patients with mild (60 ≤ creatinine clearance [CrCl] < 90 mL/min) or moderate (29 ≤ CrCl < 60 mL/min) renal impairment. No data are available in patients with severe renal impairment (15 ≤ CrCl < 29 mL/min) (see Product Monograph 10.3 Pharmacokinetics).

Hepatic impairment

No formal studies of RYBREVANT in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustment is necessary for patients with mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5 x ULN)]. No data are available in patients with moderate (total bilirubin 1.5 to 3 times ULN) or

severe (total bilirubin >3 times ULN) hepatic impairment (see Product Monograph 10.3 Pharmacokinetics).

Pediatrics (<18 years)

The safety and efficacy of RYBREVANT have not been established in pediatric patients.

Geriatrics (≥65 years)

No dose adjustment of RYBREVANT is required in patients aged 65 years or older. (see 7.1.4 Geriatrics and see Product Monograph 10.3 Pharmacokinetics).

4.3 Reconstitution

Parenteral Products: **Dilution**

RYBREVANT solution must be diluted and prepared for intravenous infusion by a healthcare professional using aseptic technique.

- Determine the dose required and number of RYBREVANT vials needed based on patient's baseline weight (see 4.2 Recommended Dose and Dosage Adjustment). Each vial of RYBREVANT contains 350 mg of amivantamab.
- Check that the RYBREVANT solution is colorless to pale yellow. Do not use if discoloration or visible particles are present.
- Withdraw and then discard a volume of either 5% dextrose [glucose] solution USP or 0.9% sodium chloride solution USP from the 250 mL infusion bag equal to the volume of RYBREVANT to be added (i.e., discard 7 mL diluent from the infusion bag for each RYBREVANT vial). Infusion bags must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).
- Withdraw 7 mL of RYBREVANT from each vial and add it to the infusion bag. The final volume in the infusion bag should be 250 mL. Each vial contains a 0.5 mL overfill to ensure sufficient extractable volume. Discard any unused portion left in the vial.
- Gently invert the bag to mix the solution. Do not shake.
- Visually inspect the diluted solution before administration. Do not use if discoloration or visible particles are observed.
- Diluted solutions should be administered within 10 hours (including infusion time of 2-5 hours, Table 7 and Table 8) at room temperature (15°C to 25°C) and in room light (see 11 Storage, Stability and Disposal).

4.4 Administration

- Due to the frequency of infusion related reactions (IRRs; see 7 Warnings and Precautions) at the first dose, RYBREVANT must be infused via a peripheral line for all Cycle 1 doses (Week 1 to Week 4) to minimize drug exposure in the event of an IRR. If peripheral access is limiting, earlier use of a central line in Cycle 1 starting after Cycle 1 Day 8 may be considered if deemed medically acceptable.
- RYBREVANT via a central line may be considered for subsequent weeks.

- For the first dose, RYBREVANT should be diluted as close to administration as possible to allow for maximal flexibility for infusion time and allow for IRR management.
- Prior to administration, prime the infusion set with the diluent (either 5% dextrose solution or 0.9% sodium chloride solution).
- Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.2 micrometer), primed with diluent only. Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
- Do not infuse RYBREVANT concomitantly in the same intravenous line with other agents.
- This medicinal product is for single use only. Any unused medicinal product should be disposed of in accordance with local requirements.

RYBREVANT in combination with carboplatin and pemetrexed

- Administer RYBREVANT, when used in combination with carboplatin and pemetrexed, intravenously at the recommended dose as per Table 1 and according to the infusion rates in Table 7.
- When used in combination with carboplatin and pemetrexed, RYBREVANT is administered weekly for the first four weeks. Patients do not receive RYBREVANT treatment in Week 5 or 6. RYBREVANT is administered at Week 7 and every 3 weeks thereafter.
- Administer treatment in the following order: pemetrexed infusion first, carboplatin infusion second, and the RYBREVANT infusion last according to Table 2.

Table 7: Infusion Rates for RYBREVANT when in combination with carboplatin and pemetrexed

Body Weight Less than 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate**	**Subsequent Infusion Rate†**
Week 1 (split dose infusion)			
Week 1 Cycle 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 Cycle 1 *Day 2*	1050 mg	33 mL/hr	50 mL/hr
Week 2 Cycle 1 *Day 8*	1400 mg	65 mL/hr	
Week 3 Cycle 1 *Day 15*	1400 mg	85 mL/hr	
Week 4 Cycle 2 *Day 1*	1400 mg	125 mL/hr	
Week 5 and 6	No dose		

Week 7 Cycle 3 *Day 1* **and Subsequent weeks***	1750 mg	125 mL/hr	
Body Weight Greater Than or Equal to 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate**	**Subsequent Infusion Rate†**
Week 1 (split dose infusion)			
Week 1 Cycle 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 Cycle 1 *Day 2*	1400 mg	25 mL/hr	50 mL/hr
Week 2 Cycle 1 *Day 8*	1750 mg	65 mL/hr	
Week 3 Cycle 1 *Day 15*	1750 mg	85 mL/hr	
Week 4 Cycle 2 *Day 1*	1750 mg	125 mL/hr	
Week 5 and 6	No dose		
Week 7 Cycle 3 *Day 1* **and Subsequent weeks***	2100 mg	125 mL/hr	

* Starting at Week 7 (start of Cycle 3), patients are dosed every 3 weeks.

† Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of infusion related reactions.

RYBREVANT monotherapy

- Administer RYBREVANT as a monotherapy at the recommended dose as per Table 3 and according to the infusion rates in Table 8.
- As a monotherapy, RYBREVANT is administered weekly for the first four weeks. RYBREVANT is then administered at Week 5 and every 2 weeks thereafter.

Table 8: Infusion Rates for RYBREVANT monotherapy

Body Weight Less Than 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate**	**Subsequent Infusion Rate†**
Week 1 (split dose infusion)			
Week 1 Cycle 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 Cycle 1 *Day 2*	700 mg	50 mL/hr	75 mL/hr
Week 2 Cycle 1 *Day 8*	1050 mg	85 mL/hr	
Week 3 Cycle 1 *Day 15*	1050 mg	125 mL/hr	
Week 4 Cycle 1 *Day 22*	1050 mg	125 mL/hr	

Week 5 Cycle 2 *Day 1* **and subsequent weeks/cycles***	1050 mg	125 mL/hr	
Body Weight Greater Than or Equal to 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate**	**Subsequent Infusion Rate†**
Week 1 (split dose infusion)			
Week 1 *Day 1* Cycle 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2* Cycle 1 *Day 2*	1050 mg	35 mL/hr	50 mL/hr
Week 2 Cycle 1 *Day 8*	1400 mg	65 mL/hr	
Week 3 Cycle 1 *Day 15*	1400 mg	85 mL/hr	
Week 4 Cycle 1 *Day 22*	1400 mg	125 mL/hr	
Week 5 Cycle 2 *Day 1* **and subsequent weeks/cycles***	1400 mg	125 mL/hr	

* Starting at week 5 (start of Cycle 2), patients are dosed every 2 weeks.

† Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of infusion related reactions.

4.5 Missed Dose

If a planned dose of RYBREVANT is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.

5 Overdose

There is no information on overdosage with RYBREVANT. There is no known specific antidote for RYBREVANT overdose. In the event of an overdose, stop RYBREVANT, monitor patient for any signs or symptom of adverse reactions and undertake general supportive measures until clinical toxicity has diminished or resolved.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of biologic products, healthcare professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 9: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous (IV) infusion	Liquid concentrate for IV infusion 350mg/7mL	EDTA disodium salt dihydrate, L-Histidine, L-Histidine hydrochloride monohydrate, L--Methionine, Polysorbate 80, Sucrose, Water for Injection

RYBREVANT is available as a colourless to pale yellow preservative-free liquid concentrate for intravenous infusion after dilution.

Each single-use vial contains 350 mg of amivantamab per 7 mL (or 50 mg of amivantamab per mL). Each vial is individually packaged in a carton.

7 Warnings and Precautions

General

The safety data described in the 7 Warnings and Precautions section reflects the safety profile of 281 patients with locally advanced or metastatic non small cell lung cancer (NSCLC) including 130 patients who received RYBREVANT in combination with carboplatin and pemetrexed in the MARIPOSA-2 study and 151 patients who received RYBREVANT in combination with carboplatin and pemetrexed in the PAPILLON study.

The safety data described in the 7 Warnings and Precautions section also reflects exposure of 302 patients, with locally advanced or metastatic NSCLC to RYBREVANT monotherapy in the CHRYSALIS study. This includes 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. Patients were treated at a dose of 1050 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) once weekly for 4 weeks, then every 2 weeks starting at Week 5.

Carcinogenesis and Genotoxicity

No animal studies have been performed to evaluate the carcinogenic or mutagenic potential of amivantamab (see Product Monograph 16 Non-Clinical Toxicology).

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

If patients experience treatment-related symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

Immune

Infusion related reactions may occur in patients treated with RYBREVANT. The most frequent signs and symptoms include chills, nausea, dyspnea, flushing, chest discomfort, hypotension, and vomiting.

RYBREVANT in combination with carboplatin and pemetrexed

Infusion related reactions (IRRs) occurred in 49.5% of patients treated with RYBREVANT. Among patients receiving treatment on Week 1 Day 1, 45.7% experienced an IRR, while the incidence of IRR was 1.5% with the Day 2 infusion, 2.1% with the Week 2 infusion, and cumulatively 8.2% with subsequent infusions. Of the cases that reported IRRs, 93.5.% were Grade 1-2, 6.5% were Grade 3, and 0% were Grade 4. The median time to onset was 1.0 hours (range 0.0 to 7 hours) after start of infusion. The incidence of dose reduction due to IRR was 0.4%, and 2.8% of patients permanently discontinued RYBREVANT due to IRR.

RYBREVANT as monotherapy

Infusion related reactions (IRRs) occurred in 66% of patients treated with RYBREVANT. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the cases that reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62.3% and 1.3% of patients permanently discontinued RYBREVANT due to IRR.

Prior to initial infusion (Week 1) of RYBREVANT, administer antihistamines, antipyretics, and glucocorticoids to reduce the risk of IRRs. For subsequent doses, administer antihistamines and antipyretics. Administer the initial infusion of RYBREVANT in split doses on Week 1, Day 1, and Day 2. Administer RYBREVANT via a peripheral line for all Cycle 1 doses (Week 1 to Week 4) (see 4 Dosage and Administration).

To reduce the risk of infusion related reactions, administer pre-infusion oral dexamethasone starting 2 days prior to the initial infusion followed by the recommended pre-infusion medications to be administered on the day of initial infusion (Table 4) (see 4 Dosage and Administration, Pre-infusion medications). The addition of oral dexamethasone demonstrated a reduction in incidence and severity of IRRs on the day of the initial infusion.

Treat patients with RYBREVANT in a setting with appropriate medical support necessary to treat IRRs. Interrupt RYBREVANT infusion at the first sign of IRRs and institute post-infusion medication as clinically indicated. Upon resolution of symptoms, resume the infusion at 50% of the previous rate. For recurrent Grade 3 or 4 IRRs, permanently discontinue RYBREVANT (see 4 Dosage and Administration).

Ophthalmologic

Eye disorders may occur in patients treated with RYBREVANT.

RYBREVANT in combination with carboplatin and pemetrexed

Eye disorders, including keratitis (0.4%), occurred in 10.7% of patients treated with RYBREVANT. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, visual impairment, ocular hyperemia, aberrant eyelash growth, conjunctival hyperemia, blepharitis, and uveitis. All events were Grade 1-2.

RYBREVANT as monotherapy

Eye disorders, including keratitis (0.7%), occurred in 13.2% patients treated with RYBREVANT. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, lacrimation increased, visual impairment, ocular hyperemia, eyelid ptosis, aberrant eyelash growth, and uveitis. All events were Grade 1-2.

Refer patients presenting with worsening eye symptoms promptly to an ophthalmologist and advise discontinuation of contact lenses until symptoms are evaluated. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity (see 4 Dosage and Administration).

Reproductive Health: Female and Male Potential

Due to the risk that RYBREVANT can cause fetal harm when administered to pregnant women, advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT (see 7.1.1 Pregnancy). Male patients must use effective contraception (e.g., condom) and not donate or store semen during treatment and for 3 months after the last dose of RYBREVANT.

- **Fertility**

  No data are available to determine potential effects of RYBREVANT on fertility in males or females (see 7.1.1 Pregnancy).

- **Teratogenic Risk**

  Administration of other EGFR and MET inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryolethality, and abortion. Therefore, based on its mechanism of action and findings in animal models, RYBREVANT could cause fetal harm when administered to a pregnant woman (also see 7.1.1 Pregnancy).

Respiratory

Interstitial lung disease (ILD/pneumonitis may occur in patients treated with RYBREVANT.

RYBREVANT in combination with carboplatin and pemetrexed

Interstitial lung disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) occurred in 2.1% of patients treated with RYBREVANT, with 1.8% of patients experiencing Grade 3 ILD. Six patients (2.1%) discontinued RYBREVANT due to ILD/pneumonitis.

RYBREVANT as monotherapy

ILD or ILD-like adverse reactions (e.g. pneumonitis) occurred in 3.3% of patients treated with RYBREVANT, with 0.7% of patients experiencing Grade 3 ILD. Three patients (1%) discontinued RYBREVANT due to ILD/pneumonitis.

Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from the clinical studies.

Monitor patients for symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). If symptoms develop, interrupt treatment with RYBREVANT pending investigation of these symptoms. Evaluate suspected ILD and initiate appropriate treatment as necessary. Discontinue RYBREVANT in patients with confirmed ILD (see 4 Dosage and Administration).

Skin

Skin and nail reactions may occur in patients treated with RYBREVANT.

RYBREVANT in combination with carboplatin and pemetrexed

Rash (including dermatitis acneiform) (81.9%), pruritus (10.7%) and dry skin (15.7%) occurred in patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3 events occurring in 15.3% of patients. Rash leading to dose reduction occurred in 13.5% of patients, and RYBREVANT discontinuation due to rash occurred in 2.5% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days (range: 1 to 311 days). Nail toxicity occurred in patients treated with RYBREVANT. All events were Grade 1 or 2, with Grade 3-4 nail toxicity occurring in 0% of patients.

RYBREVANT as monotherapy

Rash (including dermatitis acneiform) (73.5%), pruritis (17.9%) and dry skin (10.9%) occurred in patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3 events occurring in 3.6% of patients. Rash leading to dose reduction occurred in 5% of patients and RYBREVANT discontinuation due to rash occurred in 0.7% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days (range: 1 to 276 days). Paronychia occurred in patients treated with RYBREVANT. Most events were Grade 1 or 2, with Grade 3 paronychia occurring in 1.4% of patients.

Toxic epidermal necrolysis (TEN) occurred in one patient (0.2%) treated with RYBREVANT. Permanently discontinue RYBREVANT if TEN is confirmed.

A prophylactic approach to rash prevention should be considered. Instruct patients to limit sun exposure during and for 2 months after RYBREVANT therapy. Protective clothing and use of sunscreen are advisable. Alcohol-free emollient cream is recommended for dry areas with the use of RYBREVANT. If skin or nail reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 or poorly-tolerated Grade 2 events, add systemic antibiotics and oral steroids and consider dermatologic consultation. For Grade 4 skin

reactions, permanently discontinue RYBREVANT. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce, or permanently discontinue RYBREVANT based on severity (see 4 Dosage and Administration).

7.1 Special Populations

7.1.1 Pregnancy

There are no human or animal data to assess the risk of RYBREVANT in pregnancy. Administration of other EGFR and MET inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryolethality, and abortion. Therefore, based on its mechanism of action and findings in animal models, RYBREVANT could cause fetal harm when administered to a pregnant woman.

RYBREVANT should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh potential risks to the fetus. If the patient becomes pregnant while taking this drug, the patient should be informed of the potential risk to the fetus.

7.1.2 Breast-feeding

No studies have been conducted to determine if RYBREVANT is excreted in human or animal milk or affects milk production. RYBREVANT is a fully human, Immunoglobulin G1 (IgG1) based bispecific antibody. In general, human IgGs are known to be excreted in breast milk during the first few days after birth, which decreases to lower concentrations soon afterwards. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed infants, advise women not to breast-feed during treatment with RYBREVANT and for 3 months following the last dose of RYBREVANT.

7.1.3 Pediatrics

The efficacy and safety of RYBREVANT in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Of the 281 patients treated with RYBREVANT in PAPILLON and MARIPOSA-2, 38% were 65 years of age or older, and 9% were 75 years of age or older. No clinically relevant differences in effectiveness were observed based on age. Adverse events that led to discontinuation of any study agent were reported for 13.8% of patients under 65 years old and 33.6% of patients aged 65 years or older.

Of the 302 patients treated with RYBREVANT in CHRYSALIS (EDI1001), 39.4% were 65 years of age or older, and 11.3% were 75 years of age or older. No clinically relevant differences in effectiveness were observed based on age. There was a higher incidence of serious adverse events observed in patients aged 65 years or older (39.5%) as compared to younger patients

(25.1%). There was also a higher incidence of adverse events leading to dose interruptions observed in patients aged 65 years or older (44.5%) as compared to younger patients (28.4%).

8 Adverse Reactions

Full Product Monograph available at innovativemedicine.jnj.com/canada

9 Drug Interactions

9.2 Drug Interactions Overview

No formal drug interaction studies have been performed.

9.3 Drug-Behavioural Interactions

Drug-behavioural interactions have not been established.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

11 Storage, Stability, and Disposal

Unopened vial:

Store in a refrigerator at 2°C to 8°C. Do not freeze. Store in the original carton in order to protect from light.

After dilution:

Since amivantamab solutions do not contain a preservative, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. Administer diluted solutions within 10 hours (including infusion time) at room temperature (15°C to 25°C) and in room light.

12 Special Handling Instructions

Do not freeze. Protect from light. This product contains no preservative. Any unused medicinal product should be disposed of in accordance with local requirements.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrRYBREVANT®

amivantamab for injection

50 mg/mL Concentrate for Solution for Infusion

This Patient Medication Information is written for the person who will be taking **RYBREVANT**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about RYBREVANT, talk to a healthcare professional.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

What RYBREVANT is used for:

- See the following boxed text

RYBREVANT is used in adults with a type of cancer called 'non-small cell lung cancer'. It is used when the cancer has spread in your body and has gone through certain genetic changes (EGFR Exon 19 deletions, Exon 21 L858R substitution mutations, or Exon 20 insertion mutations) in a gene called 'epidermal growth factor receptor' (EGFR).

For the following indication, RYBREVANT has been approved **with conditions (NOC/c)**. This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to verify RYBREVANT's clinical benefit. For more information, talk to your healthcare professional.

RYBREVANT can be prescribed for you:

- after chemotherapy stops working against your cancer.

For the following indications, RYBREVANT has been approved **without conditions**. This means it has passed Health Canada's review and can be bought and sold in Canada.

RYBREVANT can be prescribed for you:

- in combination with chemotherapy after osimertinib stops working against your cancer.
- as the first medicine you receive for your cancer in combination with chemotherapy.

How RYBREVANT works:

Amivantamab is an antibody, that is a type of protein, that has been designed to recognise and attach to specific targets in the body. Amivantamab targets two proteins found on cancer cells:

- Epidermal growth factor receptor (EGFR), and
- Mesenchymal-epithelial transition factor (MET).

RYBREVANT works by attaching to these proteins. This may help to slow or stop your lung cancer from growing. It may also help to reduce the size of the tumour.

RYBREVANT may be given in combination with other anti-cancer medicines. It is important that you also read the package leaflets for these other medicines. If you have any questions about these medicines, ask your doctor.

The ingredients in RYBREVANT are:

Medicinal ingredients: Amivantamab

Non-medicinal ingredients: Ethylenediaminetetraacetic acid (EDTA), L-histidine, L-methionine, polysorbate 80, sucrose, and water for injection

RYBREVANT comes in the following dosage forms:

Liquid concentrate for intravenous infusion, 350 mg / 7 mL vial

Do not use RYBREVANT if:

- you are allergic to amivantamab or any other ingredients of RYBREVANT (see "The ingredients in RYBREVANT are:")

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RYBREVANT. Talk about any health conditions or problems you may have, including if you:

- have a history of lung or breathing problems
- have suffered from inflammation of your lungs (a condition called "interstitial lung disease" or "pneumonitis")

Other warnings you should know about:

Infusion related reactions: Before each infusion of RYBREVANT, you will be given medicines which help to lower the chance of infusion related reactions. These may include:

- Medicines for an allergic reaction (antihistamines)
- Medicines for inflammation (corticosteroids)
- Medicines for fever (such as acetaminophen)

You may also be given additional medicines based on any symptoms you may experience. If you have any further questions on the use of this medicine, ask your doctor or nurse.

Tell your healthcare professional straight away while taking RYBREVANT if you get any of the following side effects:

- Any side effect during the intravenous infusion (drip into a vein) of RYBREVANT.
- Sudden difficulty in breathing (shortness of breath), cough, or fever that may suggest inflammation of the lungs.
- Skin and nail problems. To reduce the risk of skin problems, keep out of the sun, wear protective clothing, apply sunscreen, and use moisturisers regularly on your skin and nails while taking RYBREVANT. You also need to do this for 2 months after you stop treatment.
- Eye problems. If you have vision problems or eye pain contact your doctor or nurse straight away. If you use contact lenses and have any new eye symptoms, stop using contact lenses and tell your doctor straight away.

Children and adolescents

RYBREVANT should not be given to children or young people below 18 years of age. This is because it is not known how the medicine will affect them.

Contraception

If you or your partner could become pregnant, you must use effective contraception during and for 3 months after stopping treatment with RYBREVANT.

Pregnancy and fertility – information for women

Tell your doctor or nurse before you are given RYBREVANT if you are pregnant, think you might be pregnant or are planning to have a baby.

If you become pregnant while being treated with this medicine, tell your doctor or nurse straight away. You and your doctor will decide if the benefit of having the medicine is greater than the risk to your baby.

Pregnancy and fertility – information for men

If your partner becomes pregnant while you are taking this medicine, tell your doctor straight away.

Men should not donate or store semen during and for 3 months after stopping treatment with RYBREVANT.

Breast-feeding

You should not breast-feed while taking this medicine and for 3 months after stopping treatment with RYBREVANT.

Driving and using machines

If you feel tired or feel dizzy after taking RYBREVANT, do not drive or use machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Interactions with other drugs, vitamins, minerals, natural supplements or alternative medicines have not been established with RYBREVANT.

How you are given RYBREVANT:

- RYBREVANT will be given to you by a healthcare professional in a healthcare setting.
- A nurse or doctor will give you RYBREVANT through a drip into a vein ('intravenous infusion') over several hours.

Usual dose:

Your doctor will determine your dose of RYBREVANT. The dose of RYBREVANT will depend on your body weight at the start of your therapy. In the first week your doctor will give you the RYBREVANT dose split over two days.

The usual dose of RYBREVANT when given alone is:

- 1050 mg if you weigh less than 80 kg (175 lbs).
- 1400 mg if you weigh more than or equal to 80 kg (175 lbs).

When given alone, RYBREVANT is given as follows:

- once a week for the first 4 weeks
- then once every 2 weeks starting at Week 5 as long as you are getting benefit from the treatment.

The usual dose of RYBREVANT when given with chemotherapy, is:

- 1400 mg for the first 4 doses and 1750 mg for subsequent doses if you weigh less than 80 kg (175 lbs).
- 1750 mg for the first 4 doses and 2100 mg for subsequent doses if you weigh more than or equal to 80 kg (175 lbs).

When given with chemotherapy, RYBREVANT is given as follows:

- once a week for the first 4 weeks
- then once every 3 weeks starting at Week 7 as long as you are getting benefit from the treatment.

Other medicines given before treatment with RYBREVANT
You will be given other medicines that help to lower the chance of infusion-related reactions.

Two days before the first infusion of RYBREVANT

- Oral medicines for inflammation (Corticosteroids)

Day of Infusion of RYBREVANT

- medicines for an allergic reaction (anti-histamines)
- medicines for inflammation (corticosteroids)
- medicines for fever (such as acetaminophen)

Overdose:

This medicine will be given by your doctor or nurse. In the unlikely event that you are given too much (an overdose) your doctor will check you for side effects.

If you think you, or a person you are caring for, have taken too much RYBREVANT, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

If you miss an appointment to get RYBREVANT:

- If you miss an appointment, call your doctor and make another appointment as soon as possible
- It is very important to go to all of your appointments

Possible side effects from using RYBREVANT:

These are not all the possible side effects you may have when taking RYBREVANT. If you experience any side effects not listed here, tell your healthcare professional.

Very common side effects (may affect more than 1 in 10 people (>10%)

- Rash
- Infected skin around the nail
- Dry skin
- Itching
- Constipation or diarrhoea
- Sores in mouth
- Nausea or vomiting
- Feeling very tired
- Swollen hands, face, ankles or feet
- Decreased appetite
- Dizziness
- Fever

- Changes in eyesight
- Muscle pain
- Cough
- Shortness of breath

Common side effects (may affect between 1 and 10 people out of every 100)

- Hemorrhoids
- Stomach pain
- Muscle aches and joint pain

RYBREVANT can cause abnormal blood tests. Your doctor will decide when to perform blood tests and will interpret the results. RYBREVANT may cause:

- low level of 'albumin' in the blood
- increased level of liver enzymes 'alanine aminotransferase', 'aspartate aminotransferase', and 'gamma-glutamyltransferase' in the blood
- low level of sodium in the blood
- low number of white blood cells
- low number of red blood cells
- low number of platelets, cells that help blood to clot
- high level of 'bilirubin' in the blood
- low level of phosphate in the blood
- low level of protein in the blood
- high level of sugar in the blood
- increased level of blood lactate dehydrogenase
- increased level of 'creatinine' in the blood

Serious side effects and what to do about them

Frequency/Symptom /effect	Talk to your healthcare professional	
	Only if severe	In all cases
Very common (affecting more than 1 in 10 people)		
Infusion reactions: chills, nausea, feeling short of breath, flushing, chest discomfort, vomiting, or any side effect during an infusion. This can happen especially with the first dose.		√
Skin and Nail Problems: rash (including acne), infected skin around the nails, dry skin, itching, pain, blistering, and redness. Tell your doctor if your skin or nail problems get worse.		√
Eye Problems: dry eye, eye redness, itchy eyes, problems/changes with vision, growth of eyelashes,		√

Frequency/Symptom /effect	Talk to your healthcare professional	
	Only if severe	In all cases
inflamed cornea (front part of the eye), excessive tearing		
Common (affecting between 1 to 10 people out of every 100)		
Inflammation of the lungs: sudden difficulty in breathing, cough, or fever. This could lead to permanent damage ('interstitial lung disease')		**√**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

RYBREVANT will be stored at a hospital or clinic.

Store in a refrigerator at 2°C to 8°C. Do not freeze. Protect from light.

If you want more information about RYBREVANT:

- Talk to your healthcare professional
- For questions or concerns, please contact the manufacturer, Janssen Inc., at innovativemedicine.jnj.com/canada
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (Drug Product Database: Access the database; the manufacturer's website (innovativemedicine.jnj.com/canada), or by calling 1-800-567-3331.

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This document provides you with the most current information at the time of printing.

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